Drug allergy in mast cell disease

Knut Brockow[a] *and Patrizia Bonadonna*[b]

Purpose of review
Mastocytosis in adults is associated with a history of anaphylaxis in 22–49%. In addition, monoclonal mast cell activation syndrome has been described presenting with anaphylaxis, especially in patients with hymenoptera venom anaphylaxis. Data on patients with drug hypersensitivity and mast cell diseases are scarce.

Recent findings
Drugs are elicitors of anaphylaxis in patients with mastocytosis. Drug hypersensitivity is only seldom described as associated with undetected mast cell disease in the literature. Together with a single-centred retrospective study, this data suggests that from all patients with drug-induced anaphylaxis, probably only a minority are associated with mast cell disease. Most of these cases in the literature are related to general anaesthesia. Thus, for patients with mastocytosis, general anaesthesia appears to be a procedure associated with risk of mast cell degranulation, and special precautions should be considered.

Summary
The association between immediate drug hypersensitivity and undetected mast cell diseases appears to be moderate, but nevertheless basal serum tryptase determination and examination for skin signs of mast cell disorders are recommended. An ongoing European multicenter study by the European Network for Drug Allergy will provide more information on this topic.

Keywords
anaphylaxis, drug allergy, drug hypersensitivity, mast cell diseases, mastocytosis

INTRODUCTION

Mastocytosis is characterized by increased numbers of mast cells in the skin, the bone marrow and/or in other tissues [1▪]. Patients with systemic mastocytosis may experience symptoms due to massive mast cell activation and release of mediators (e.g. generalized pruritus, abdominal pain, and anaphylaxis). Patients with mastocytosis have an increased risk of anaphylaxis. The cumulative prevalence of anaphylaxis has been reported to be between 22 and 49% in adults and between 6 and 9% in children [2,3]. Only some patients with mastocytosis have attacks of anaphylaxis [4,5], whereas other patients may not show systemic symptoms for decades. Fatal anaphylaxis has been described as idiopathic and after hymenoptera venom stings [6].

Immunological drug hypersensitivity reactions may be divided into immediate (<1 h) and non-immediate (>1 h) reactions [7]. Immediate reactions manifest typically with urticaria or anaphylaxis. Drug hypersensitivity has been reported to be the most frequent cause of fatal anaphylaxis. However, the frequency of underlying mast cell diseases in drug hypersensitivity is unknown. This study reviews the current knowledge on mast cell disease and immediate drug hypersensitivity with an emphasis on recent literature.

SPECTRUM OF MAST CELL DISEASES

Clinical signs and symptoms of mast cell diseases may be predominantly explained by tissue mast cell hyperplasia and an excessive production of mast cell mediators [1▪]. Molecular mechanisms have been identified, linking increased releasability of mast cell mediators with high mast cell numbers. In recent years, the term mast cell activation syndrome (MCAS) has been increasingly used as a tentative diagnosis for patients with potential mast cell

[a]Department of Dermatology and Allergology, Technische Universität Munich, and Center for Allergy and Environment, Technische Universität und Helmholtz Center Munich, Munich, Germany and [b]Allergy Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Correspondence to Knut Brockow, Department of Dermatology and Allergology Biederstein, Technische Universität Munich, Biedersteiner Strasse 29, D-80802, Munich, Germany. Tel: +4989 4140 3182; e-mail: knut.brockow@lrz.tum.de

Curr Opin Allergy Clin Immunol 2012, 12:354–360
DOI:10.1097/ACI.0b013e328355b7cb

KEY POINTS

- Drugs have been implicated as triggers in patients who have mastocytosis associated with anaphylaxis in 18–25% of cases.
- General anaesthesia in patients with mastocytosis is an area of concern and requires specific consideration in the planning of the procedure.
- In unselected patients with drug hypersensitivity, only few patients with unrecognized mast cell disease have been described.
- Nevertheless, in patients with drug anaphylaxis, basal serum tryptase determination and careful skin inspection is recommended to exclude mast cell disease.

mediator-related signs and symptoms. Recently, a proposal for a mast cell disease classification has been published as a result of a consensus meeting [8▪▪]. According to this proposal (Fig. 1), primary mast cell activation encompasses both mastocytosis and monoclonal mast cell activation syndrome (MMAS). The major criterion for mastocytosis is the demonstration of multifocal mast cell clusters in the bone marrow or in biopsies of other tissues. Minor criteria include a basal tryptase level of more than 20 ng/ml, atypical mast cell morphology, aberrant expression of CD25 and CD2 on mast cells and the detection of a Codon 816 mutation in the gene *c-kit*. According to current guidelines, at least the major criterion and one minor or three minor criteria are needed for the diagnosis of mastocytosis [1▪]. In addition, a group of patients with hymenoptera venom or idiopathic anaphylaxis, but not drug-induced anaphylaxis, has been described which demonstrates one or two, but not sufficient minor criteria for mastocytosis. It has been agreed that these patients have MMAS [8▪▪].

Secondary mast cell activation typically occurs in allergic diseases, and trigger factors can be found in this category. It also occurs in patients with chronic autoreactive or physical urticaria.

Idiopathic mast cell activation occurs in chronic idiopathic urticaria or angioedema and in idiopathic anaphylaxis. In addition, the presence of a distinct idiopathic mast cell activation syndrome (MAS) has been proposed as a preliminary checkpoint, if a final diagnosis can otherwise not be made and criteria for this condition have been formulated [8▪▪].

Frequency of drug anaphylaxis in patients with mastocytosis

In patients with mastocytosis, the cumulative prevalence of a history compatible with anaphylaxis has been reported to be 49% in adults and 9% in children [3]. Anaphylaxis was associated with systemic disease and higher baseline tryptase values. In another study [2], the frequency of anaphylaxis in adults and children was reported to be 22 and 6%, respectively.

In these two studies, drugs are among the listed trigger factors for anaphylaxis. There are no data on drug-induced urticaria alone. Nonsteroidal anti-inflammatory drugs, β-lactam antibiotics, contrast

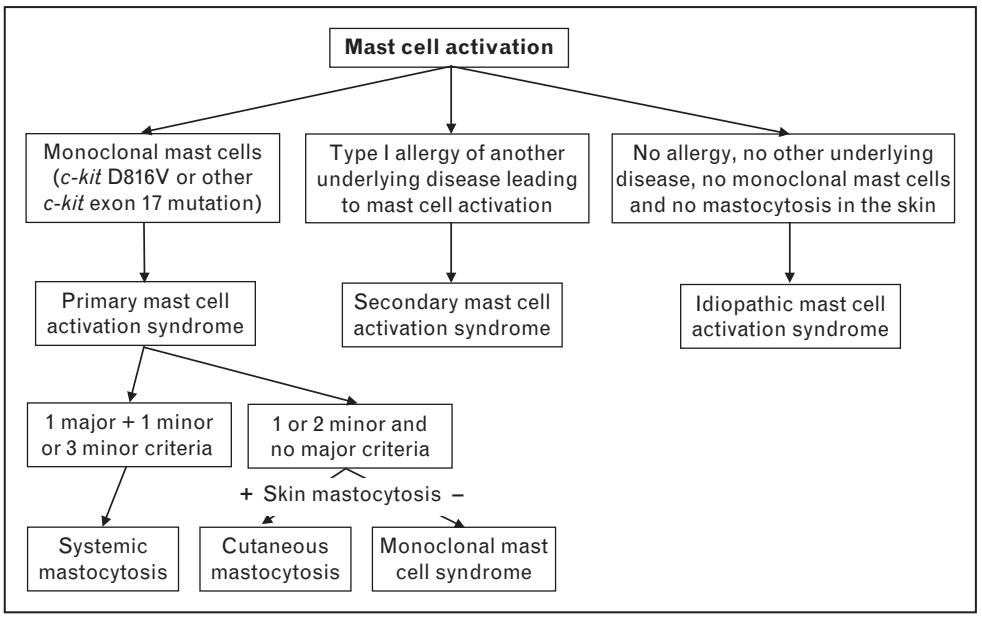

FIGURE 1. Classification proposal for mast cell activation disorders. Adapted from [8▪▪].

media, aminoglycosides, streptomycin, phenylephrine, codeine, local anaesthetic, and general anaesthesia have been listed as trigger factors in the history of the patients [2,3]. However, a formal confirmation by positive skin test or provocation test has not been described in these publications.

Mast cell disease in studies of patients with drug hypersensitivity

In patients with anaphylaxis, selected studies have looked for undetected mast cell disease. Bonadonna *et al.* [9▪▪] have studied the frequency of mast cell disease in patients with food or drug induced severe systemic reactions including anaphylaxis. In contrast to preliminary studies in patients with hymenoptera sting allergy, where 11.6% of patients with systemic reactions had increased serum basal tryptase levels and primary mast cell activation syndrome was detected in 88.2% of further analyzed patients [5], the association between severe systemic reactions to drugs and mast cell disease was weaker. Out of a total of 86 patients with drug hypersensitivity, seven patients (8.1%) had increased serum tryptase levels more than 11.4 ng/ml. However, in only one out of five bone marrow tested patients a clonal mast cell disorder was detected, and a systemic mastocytosis was diagnosed (Fig. 2). No case of MMAS was documented. The characteristics of the patients are listed in Table 1.

These data were confirmed in another recent study by Alvarez-Twose *et al.* [10▪▪] who analyzed the clinical, biological, and molecular characteristics of 83 patients with anaphylaxis and other symptoms attributable to mast cell mediator release

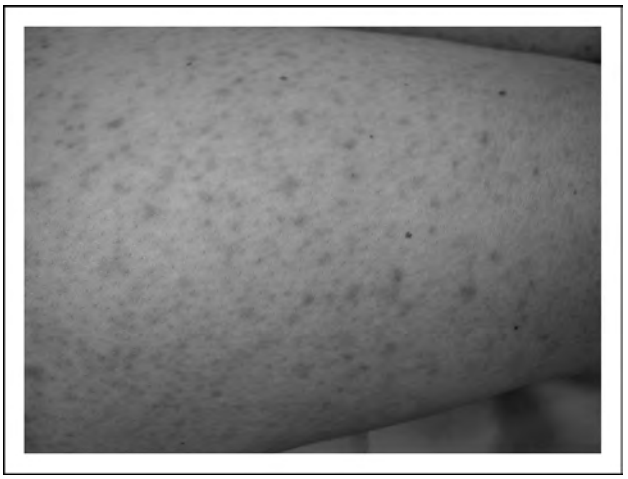

FIGURE 2. Inconspicuous red brown maculae in a patient with anaphylaxis to acetylsalicylic acid, in whom further work-up revealed urticaria pigmentosa and indolent systemic mastocytosis. A skin examination should be performed in patients with drug anaphylaxis to exclude mastocytosis in the skin.

Table 1. Characteristics of patients with systemic hypersensitivity reactions from drugs and increased basal serum tryptase levels

Pt	Age (years)	Sex	Culprit drug	Symptoms	Onset of symptoms (minutes)	Serum tryptase ng/mL	BM biopsy (major criteria)	BM mast cells $CD25^+$ and/or $CD2^+$	Activating KIT mutation (BM)	Spindle shaped mast cells (>25%)	Diagnosis of mastocytosis
1	37	F	Acetylsalicylic acid	Anaphylaxis	15	13.2	Positive	Positive	Positive	Positive	ISMs+
2	47	F	β-lactam antibiotic	Dyspnea, urticaria	5	16.1	Negative	Negative	Negative	Negative	Negative
3	38	M	Acetylsalicylic acid, Ketoprofen	Anaphylaxis with loss of consciousness	5	19.1	Negative	Negative	Negative	Negative	Negative
4	71	F	Cloramphenicol	Anaphylaxis	15	19.5	Negative	Negative	Negative	Negative	Negative[a]
5	65	M	Radiocontrast media	Anaphylaxis with loss of consciousness	10	20.1	Negative	Negative	Negative	Negative	Negative[a]
6	63	F	Clorhexidine, betadine	Anaphylaxis	15	26.9	n.d.	n.d.	n.d.	n.d.	–
7	8	M	Ceftriaxone	Anaphylaxis with loss of consciousness	5	26.1	n.d.	n.d.	n.d.	n.d.	–

BM, bone marrow; F, female; M, male; n.d., not done; pt, patients.
[a]Only increased normal mast cells, ISMs+: indolent systemic mastocytosis with mastocytosis in the skin.

in absence of mastocytosis-associated skin lesions. Clonality was demonstrated in 51 patients, with the majority fulfilling the criteria for systemic mastocytosis. The remaining 32 patients have symptoms of mast cell activation but without clonal mast cell disease. In patients with clonal mast cell disorders the most common trigger for anaphylactic episodes is hymenoptera sting, whereas drugs were mostly involved as a trigger in nonclonal mast cell disorder.

In other recent studies [11–14] on drug hypersensitivity, which included serum tryptase measurements after reactions, but did not look specifically at mast cell disease, we have found no description of primary mast cell diseases.

Mast cell disease in case reports of patients with drug hypersensitivity

Only few case reports have been published recently. Renauld *et al.* [15] reported a 69-year-old woman who developed generalized erythema, arterial hypotension, and tachycardia following medication with hydroxycine, sufentanil, propofol, and atracurium during general anaesthesia for hysterectomy. In this patient, urticaria pigmentosa was detected and elevated basal serum tryptase levels indicated a probable systemic mastocytosis, whereas no confirmation was attempted. The skin tests and the basophil activation test afterwards did not show any positive results.

Bilo *et al.* [16] described two patients with mastocytosis and severe intraoperative anaphylaxis. The first patient had highly elevated basal serum tryptase levels of more than 200 ng/ml and urticaria pigmentosa, but refused a bone marrow biopsy. The second case was a 57-year-old woman who developed a biphasic anaphylaxis with urticaria and hypotension not only intraoperatively, but also 14 h after resolution of the first episode. The patient had basal serum tryptase concentrations of 36–42 ng/ml and indolent systemic mastocytosis was confirmed by bone marrow biopsy. In both patients, skins tests to interoperatively given medications were negative; however, in the second patient anaphylaxis due to penicillin allergy was suspected, because of demonstration of low level of specific IgE antibodies to penicillins.

Anaphylaxis in children with mastocytosis is rare and most often associated with severe cutaneous, especially bullous disease [17]. A recent case report [18] of anaphylaxis during general anaesthesia in a 13-year-old girl was attributed to mastocytosis. The girl was anaesthetized for orthopaedic surgery with midazolam, fentanyl, lidocaine, and propofol. Two minutes after the subsequent administration of cefazolin, the patient developed wheezing, a generalized rash, and hypotension. This was treated with multiple doses of epinephrine, diphenhydramine, dexamethasone, ranitidine, and endotracheal intubation. Four hours later the patient had another episode of emesis, dyspnea and hypotension which required further treatment. The authors called the underlying condition 'systemic mastocytosis' only because of persistent elevation of serum tryptase levels between 17 and 18 ng/ml [18]. However, this diagnosis is incorrect as the bone marrow aspirate and biopsy did not show aggregations of mast cells, and further criteria had not been looked for. Thus, the correct diagnosis should have been biphasic anaphylaxis during general anaesthesia associated with persistent elevation of serum tryptase levels, but without a demonstration of any major or minor criteria for systemic mastocytosis. An allergological evaluation to detect the culprit medication (especially cefazolin) was not performed.

In addition to reactions to general anaesthesia or antibiotics, anaphylaxis to an iodinated contrast medium has been described in a 43-year-old woman [19]. Persistently elevated tryptase levels led to further evaluation and the eventual confirmation of systemic mastocytosis. Another recent case report highlights and describes the phenomenon of acetylsalicylic acid-augmented summation anaphylaxis in mastocytosis, which has been described before [20]. A 20-year-old man reported taking acetylsalicylic acid to relieve a headache. Two hours later he ate two raw carrots, and after 15 min developed flushing, dizziness, and respiratory distress. In this case, oral allergy syndrome to raw carrots was confirmed by provocation test, but only after combined exposure to acetylsalicylic acid 60 min before the consumption of carrots. Following the medication alone, he only developed generalized flushing and feeling of warmth.

We have not found any case in the literature with monoclonal mast cell activation syndrome associated with drug urticaria or anaphylaxis.

What is the best anaesthetic management in patients with mastocytosis?

Recent guidelines on anaphylaxis associated with anaesthesia give no guidance on the management of patients with mastocytosis [21▪▪,22].

Anaesthesia in childhood mastocytosis

Anaphylaxis in children with paediatric-onset mastocytosis is rare. In one study [3] it was limited to patients with extensive skin disease (>40% of body surface) and associated with higher serum tryptase

levels, but nonexistent for children with mastocytosis and limited macular lesions.

In a retrospective case series of patients with paediatric mastocytosis that includes 24 general anaesthesias and five cases of sedation and local anaesthesia in 22 patients at the National Institute of Health, Bethesda, Maryland, USA, no prophylactic H_1 and H_2 blockers and steroids were given, whereas chronic maintenance therapy was continued in 13 cases [23]. These cases included eight children with systemic mastocytosis and 13 patients with serum tryptase levels more than 20 ng/ml. Fifteen patients were sedated with midazolam. No overt restriction of the anaesthetic technique had been reported. Adverse reactions were limited to flushing in 9% and gastrointestinal reactions with nausea, vomiting, and/or diarrhea in 18% of patients.

Another recent case series of six patients with cutaneous mastocytosis requiring general anaesthesia added to the results of this study [24]. Premedication was given in two patients only and no complications occurred in this series.

Combining all available data on the risk of anaphylaxis in children with paediatric-onset mastocytosis, the risks of general anaesthesia appear to be overstated by mastocytosis websites [24]. In patients without excessive spreading of skin disease and/or systemic disease an increased risk appears doubtful. Even in these patients, however, the anaesthetist should have a thorough understanding of mastocytosis and its manifestations. He must be informed about the form of mastocytosis, basal serum tryptase levels as a marker of the total mast cell load, previous anaphylactic episodes, and, if applicable, present mast cell activation status (e.g. pruritus during viral infection, active blistering disease). Children with extensive skin disease and especially active disease forming blisters, however, should be anaesthetized with caution (same as in adults). The anaesthetist should be prepared for emergency treatment. It is prudent, if possible, to recommend the administration of incremental dose infusion rather than single boluses of needed drugs (opioids, muscle relaxants) known to activate mast cells. Any regular maintenance medication taken to maintain mast cell stability and limit the effects of mast cell mediators should be continued during the operation. Potential trigger factors such as temperature change in the patient, infusion of cold solutions, trauma to tissue, friction and other mechanical factors, and stress should be avoided. Mast cell degranulation can be triggered by anxiety and premedication with sedatives like benzodiazepines should be considered. Before more data are available on the tolerance of NSAIDs in children with mastocytosis, a cautious approach is reasonable. Graded provocation tests should be carried out if tolerance is unclear. On the basis of available published data, the use of histamine releasing drugs during anaesthesia has not been associated with an increased number of reactions in patients with paediatric-onset mastocytosis. However, where a range of equally effective drugs is available, those with minimal histamine release should be selected, for example, fentanyl and vecuronium instead of morphine and atracurium or mivacurium.

Anaesthesia in adult patients with mastocytosis

The general principles listed for children also apply for adults, but, as more cases are reported in the literature, there may be a higher risk involved in adult patients with mastocytosis [24]. However, the data are still insufficient to clarify, whether the severity of the reaction during anaesthesia is increased due to the higher mast cell load, and/or whether the frequency of reactions is higher in comparison to the general population. In most case reports on anaphylaxis to drugs in adults with mastocytosis during a general anaesthesia, the underlying disease was not known to the anaesthetist and probably precautions were not taken. On the contrary, there have been reports about successful anaesthesia in adult patients with systemic mastocytosis, for example, with aortic valve replacement, when the procedure has been properly prepared [25].

There is insufficient empirical data in the literature on the risk associated with specific medications and the value of premedication. However, a cautious approach would include avoiding known mast cell releasing drugs in patients with mastocytosis, if others are available and can be used without compromise (Table 2) [26].

Induction agents are generally regarded as well tolerated (thiopental is associated with the highest number of reports) and inhalant anaesthetics of the fluran family have not been associated with anaphylaxis [21▪▪].

Concerning muscle relaxants, those with highest unspecific histamine release are atracurium and mivacurium. In addition, rocuronium and succinylcholin have been described to be associated with the highest number of allergic reactions [21▪▪]. Vecuronium, pancuronium, and cisatracurium have not been reported to induce a high number of reactions perioperatively.

Opioids such as morphine and codeine have been associated with anaphylaxis in patients with mastocytosis and should be avoided, if possible.

Table 2. Drug recommendations in general anaesthesia in patients with mastocytosis

	Opioids	Hypnotics	Muscle relaxants	Volatile anaesthetics
Avoid, if other agents can be used that are equally effective	Morphine Codeine	Thiopental	Succinylcholine Mivacurium Rocuronium Atracurium	
Low Risk	Fentanyl Sufentanil Remifentanil Alfentanil	Midazolam Propofol Etomidate Ketamine	Cis-Atracurium Pancuronium Vecuronium	Desflurane Sevoflurane Enflurane Isoflurane

Adapted from [26].

Fentanyl and the related agents remifentanyl, sufentanyl, and alfentanyl have not been associated with a high risk of reactions [21▪▪].

For local anaesthesia there are not enough data to support an increased risk of patients with mastocytosis. Thus, local anaesthetics, especially of the amide type, may be used. One author suggested that ropivacaine can be used, whereas bupivacaine and lidocaine could cause anaphylactoid reactions, but data supporting this statement are lacking [27]. Concerning analgesia, only few patients with mastocytosis develop an idiosyncratic reaction to nonsteroidal anti-inflammatory drugs; however, in these patients very severe reactions may occur [28]. Medications previously and continuously tolerated by the patients are allowed. However, if the tolerance of an analgesic drug is unknown, a graded provocation test should be performed at a specialized centre under close supervision.

The value of antiallergic premedication is unknown. Even despite premedication, severe reactions may occur. A reasonable, but unproven approach would be to consider premedication with an intravenously given antihistamine (dimethinden or other) 1 h before anaesthesia ± corticosteroids (e.g. prednisone 60 mg: 13, 7 and 1 h before anaesthesia) to the discretion of the anaesthetist. The value of adding an H_2 blocker (e.g. ranitidine 1 h before anaesthesia) remains unknown.

Anaesthetic management of mastocytosis patients in labour

Stress and mechanical stimulation may trigger mastocytosis-related symptoms in patients in labour. In a recent study [29▪], 35 infants were born by vaginal delivery and 10 by Caesarean section. Labour induction for nine vaginal deliveries used oxytocine ($n = 8$) or dinoprostone ($n = 1$). Prophylactic antiallergic therapy was given in 38% of cases at the discretion of the anaesthetist, using different combinations of antihistamines and corticosteroids. Anaesthetic procedures for labour and delivery were applied in 82% of cases, including epidural ($n = 32$), local ($n = 3$), and general ($n = 2$) anaesthesia. During or immediately after labour in 11% of patients symptoms were recorded and included pruritus ($n = 2$), generalized erythema ($n = 2$), and flushing ($n = 1$). Only one of these cases was treated with antimediator therapy. In three of these cases an epidural anaesthesia was administered. As in earlier reports, anaesthetic procedures and drugs given for inducing labour appear to be quite well tolerated for use in pregnant women with mastocytosis. It seems reasonable to consider premedication for pregnant mastocytosis patients during the initiation of labour, at least in patients with more severe disease.

CONCLUSION

Drug-induced anaphylaxis occurs in patients with mastocytosis; however, the association between mastocytosis and drug anaphylaxis does not appear as strong as to hymenoptera venom anaphylaxis. In patients with drug hypersensitivity, an associated monoclonal mast cell activation syndrome has not been described.

From available data on anaesthesia in patients with mastocytosis it can be concluded that the risk for children with paediatric onset mastocytosis appears limited and prophylactic antiallergic premedication is not obligatory. The anaesthetist should be informed and prepared for an emergency situation and should try to avoid possible trigger factors. In adults, with mastocytosis a few severe reactions have been reported. Anaesthetic agents to be administered to a patient need to be carefully selected, and antiallergic premedication should be

considered depending on the risk of the individual patient.

Acknowledgements

We thank Dr Roberta Zanotti for her helpful comments and support in preparing the manuscript.

Conflicts of interest

There are no conflicts of interest.

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